The Pharmacokinetics of Escitalopram in Patients With Hepatic Impairment

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ABSTRACT

The effect of hepatic impairment on the pharmacokinetics of escitalopram was determined by means of nonlinear mixed effect modeling, considering both the Child-Pugh classification (and its components) and cytochrome P450 2C19 (CYP2C19) activity. Twenty-four subjects were grouped according to their Child-Pugh score as healthy, with mild hepatic impairment or with moderate hepatic impairment. The subjects were administered a single oral dose of escitalopram 20 mg, and blood was sampled up to 168 hours after dosage. The serum concentration of escitalopram was determined and the pharmacokinetics assessed by nonlinear mixed effect modeling. The CYP2C19 activity was measured from the urinary excretion ratio of S/R-mephenytoin. All subjects tolerated the treatment well, and no serious adverse events were reported. Predicted mean area under the curve from zero to infinity (AUC_{inf}) values were 51% and 69% higher for patients with mild and moderate hepatic impairment (Child-Pugh classification), respectively, compared with healthy subjects. The best-fitting model showed an influence of CYP2C19 activity on clearance and body weight on the volume of distribution for escitalopram. CYP2C19 activity is a better predictor of escitalopram clearance than is Child-Pugh classification.

KEYWORDS: CYP2C19, escitalopram, hepatic impairment, pharmacokinetics, nonlinear regression

INTRODUCTION

When a drug is metabolized by the liver to a substantial extent and the drug is likely to be used in patients with impaired hepatic function, a pharmacokinetic study in subjects with impaired hepatic function should be performed.[1,2] While the Child-Pugh classification system has traditionally been used to stratify subjects in a hepatic impairment study, the classification was not developed to predict drug elimination capacity.[2] The "Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients With Impaired Hepatic Function," from the European Agency for the Evaluation of Medicinal Products, describes an alternative approach: to administer a probe drug and to observe whether the pharmacokinetics of the probe drug is altered. This probe would have to be sensitive enough to identify a range of severity in subjects with hepatic impairment.[2]

Escitalopram is extensively metabolized in the liver to its principal demethylated metabolites, S-demethylcitalopram (S-DCT) and didemethylescitalopram (S-DDCT). These demethylated metabolites can undergo subsequent propionic acid derivatization mediated by monoamine oxidases A and B.[3] Demethylation of escitalopram involves the cytochrome P450 CYP2C19, CYP2D6, and CYP3A4 isozymes, and demethylation of S-DCT seems to involve CYP2D6.[4] S-DCT and S-DDCT have weak pharmacological activities in vitro and practically no activities in vivo.[5] Drug oxidation depends on liver function, and hepatic CYP450 isozyme activity is decreased by ~50% in patients with liver cirrhosis[6] and is generally altered in a population with hepatic impairment.[7,8] Adedoyin et al[9] reported a selective effect of liver impairment on the activities of specific metabolizing enzymes, with CYP2C19 being more sensitive than CYP2D6.

In most cases, pharmacokinetics in hepatic impairment studies is calculated with noncompartmental analysis, in which the pharmacokinetic parameters (eg, C_{max}, area under the curve [AUC], $t_{1/2}$) are related to the Child-Pugh classification group and/or its inherent components (serum albumin, bilirubin, and prothrombin time), to assess the liver disease's impact on the drug's pharmacokinetics. An alternative and more direct approach is to use compartmental analysis in terms of nonlinear mixed effect modeling. With this approach, data from all subjects are analyzed simultaneously, and the pharmacokinetic and statistical analyses are performed in a single step.

The aim of the present study was to determine the effect of hepatic impairment on the pharmacokinetics of escitalopram, by means of nonlinear mixed effect modeling, considering both the Child-Pugh classification (and its components) and CYP2C19 activity (S/R-mephenytoin ratio).

MATERIALS AND METHODS

The clinical part of the study was performed at APEX Research in Munich, Germany. The study was conducted

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according to the principles of the Declaration of Helsinki of 1964 and its subsequent amendments, and to the principles of Good Clinical Practice after approval by the local Independent Ethics Committee (Bayerische Landesärztekammer, Körperschaft des öffentlichen Reechts, Mühlbaurstrasse 16, 81677 Munich, Germany). Before admission to the study, all subjects gave signed informed consent after the nature and possible consequences of the study were explained.

Subjects

Three groups of Caucasian subjects with the following degrees of hepatic function were enrolled in this open study: normal hepatic function (n = 8), mild hepatic impairment (n = 8), and moderate hepatic impairment (n = 8). The subjects were stratified according to the Child-Pugh classification of hepatic function (Child-Pugh Score of 5 or 6 for mild hepatic impairment and 7 to 9 for moderate hepatic impairment).[10,11] Subjects with normal liver function were matched with the other 2 groups for age, sex, and weight to the extent possible. In all cases, hepatic impairment was due to liver cirrhosis caused by alcohol abuse. There were no apparent differences in age, body weight, or creatinine clearance among the groups (Table 1).

Included in the study were men and women between 18 and 70 years of age (inclusive) who did not have any serious illness except for medically controlled hypertension or orally treated diabetes and those problems associated with the primary diagnosis of hepatic impairment. Subjects were excluded if they were current abusers of alcohol, had severe ascites, had an acute exacerbation of liver disease as defined by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*),[12] or had signs of hepatic encephalopathy. Based on medical history and the screening results of a physical examination, electrocardiogram, and clinical laboratory tests (including a drug and alcohol screening), subjects with normal liver function were deemed to be healthy and suited to the study's purpose. All of the included subjects had a creatinine clearance of more than 80 mL/min.

All subjects were in a fasted state when they received a single oral dose of escitalopram 20 mg with 200 mL of water. Alcoholic beverages were not allowed from 48 hours prior to dosing until completion of blood sampling; furthermore, the subjects with alcohol-induced liver cirrhosis abstained from alcohol for at least 1 week prior to escitalopram administration and during the entire study period. Adverse events were reported spontaneously throughout the study. Blood pressure and heart rate in both supine and standing positions were recorded predose and at 4, 12, and 24 hours after intake of escitalopram. Hematology and biochemistry parameters were assessed before, during, and after completion of the study.

Concomitant treatment with medication known to interfere with CYP2C19 and/or CYP2D6 within the 6 weeks prior to dosing or during the study was not allowed.

CYP2C19 Phenotyping

All subjects were administered racemic mephenytoin 100 mg (Epilan), (Gerot Pharmazeutika, Vienna, Austria) and the S/R-mephenytoin serum ratio was estimated and used to characterize the CYP2C19 phenotype. Mephenytoin was given as a single oral dose between 21 and 7 days before escitalopram intake, and urine was collected 0 to 8 hours after dosing. Analysis of the S- and R-enantiomer of mephenytoin in the urine was performed by means of a validated gas chromatographic method with nitrogen phosphorous selective detection. The determination of 4′-hydroxymephenytoin was performed by high performance liquid chromatography (HPLC) mass spectrometry.[13,14] The lower limit of quantification for the assay was 0.025 µg/mL for both S- and R-mephenytoin.

Serum Analysis

Blood samples (5 mL) for drug analysis were drawn from an antecubital vein 5 minutes predose and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after escitalopram intake. After clotting, the samples were centrifuged and the serum was frozen in glass tubes at –20°C. Escitalopram in serum was analyzed using an enantioselective HPLC method with tandem mass spectroscopy (MS/MS) detection after liquid-liquid extraction. The lower limit of quantification in serum was 3.08 nmol/L.

Table 1. Characteristics of the Subjects, Divided Into Child-Pugh Classification Group*

	Normal Hepatic Function	Mild Hepatic Impairment	Moderate Hepatic Impairment
Number (men/women)	6/2	6/2	6/2
Age in years (range)	59.0 (51.0-67.0)	57.8 (48.0-68.0)	57.6 (43.0-69.0)
Weight in kg (range)	76.3 (69.0-87.0)	83.9 (63.0-97.0)	78.0 (63.0-101)
CL_{Cr} in mL/min (range)	105 (84.0-128)	120 (89.0-149)	113 (85.0-170)
Child-Pugh score (range)	ND	5.63 (5.00-6.00)	7.50 (7.00-8.00)

*ND indicates not determined; CL_{Cr}, creatinine clearance.

The racemate, citalopram, was >99% pure and was used as a reference substance. A chloro-analog of citalopram, 1-(p-chlorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalan oxalate, was used as the internal standard. HPLC-grade n-heptane and methanol were purchased from Rathburn Chemicals Ltd (Walkerburn, Scotland). Ammonium trifluoroacetate (98%) was obtained from Sigma-Aldrich (Vallensbaek, Denmark). All other chemicals were analytical grade and obtained from Merck (VWR International, Albertslund, Denmark). The water was purified by an Elgastat Maxima Apparatus (Elga Ltd, Bucks, England).

The calibration samples were prepared by spiking blank samples with a solution of RS-citalopram. The samples were processed using a liquid-liquid extraction procedure.

After alkalization with 50 µL 1N NaOH, the samples were extracted by adding 6.0 mL n-heptane, containing 1.5% isoamylalcohol, shaken for 15 minutes, and then centrifuged at 2000 g for 5 minutes. The organic layer was transferred to another test tube containing 100 µL of 0.1N HCl. Following repeated shaking and centrifugation, the organic phase was discarded and the aqueous phase was collected and evaporated to dryness.

The samples were reconstituted in 0.5 mL MeOH. Fifty µL aliquots were injected into a chromatographic system consisting of a chiral column (Cyclobond V, Astec Inc, Whippany, NJ; 250 × 4.6 mm internal diameter with 5 µm particles) operated at 20°C. The mobile phase was MeOH with 0.1% ammonium trifluoroacetate at a flow rate at 1.5 mL/min, which was split 1:50. The analytes were detected with MS/MS using positive electrospray ionization in the multiple reaction mode (MRM).

Standard curves in serum were linear in the range 3 to 300 nmol/L for escitalopram.

Pharmacokinetic and Statistical Analysis

Pharmacokinetic analysis was performed by means of nonlinear mixed effect modeling with the software NONMEM V (GloboMax, Hanover, MD) running under the Compaq Visual Fortran compiler (standard edition version 6.5). In the model-building process, the first order conditional error with interaction estimation method was used.

Initially, 4 different pharmacokinetic structural models were tested: 1-compartment with and without lag time, and 2-compartment with and without lag time. Interindividual variabilities were modeled with exponential terms. An additive error model, a proportional error model, and a combined additive and proportional error model were tested for the residual error. A diagonal covariance matrix was used; that is, covariances between the structural model parameters were assumed to be negligible.

Once the pharmacokinetic and error models were identified, the influence of subject-specific covariates on the estimated pharmacokinetic parameters was evaluated. Bayesian individual patient pharmacokinetic parameter values were calculated by the posterior conditional estimation technique.[15]

Subject-specific covariates tested were age, weight, creatinine clearance, aspartate aminotransferase, alanine aminotransferase, activated partial thromboplastin time, serum albumin, bilirubin, prothrombin time, Child-Pugh classification group, and CYP2C19 activity. Mean normalized (centered) covariate values were used. Discrimination between 2 nested covariate models was based on the objective function value (OFV). Covariates to be included in the model were tested one by one on each pharmacokinetic (PK) parameter. Only completely noncorrelated parameters, judged by visual inspection, were not tested. The covariate resulting in the largest decrease in OFV for the model was included first. After inclusion of the first covariate, the above procedure was repeated. A *P* value of .01 was used for inclusion of a covariate in the model, corresponding to a decrease in OFV of 6.64. The addition of covariates to the model continued until a decrease of 6.64 could no longer be reached. This was defined as the fully parameterized model. To determine whether all the covariates included in this model remained to provide significant influence on the overall model, the covariates were sequentially removed. The significance of each covariate was tested using the nested model criteria at the more stringent *P* value of .005, resulting in a decrease in OFV of 7.88, to avoid false-positives.

Diagnostic plots of predicted versus observed dependent variable, weighted residuals versus the predicted dependent variable, weighted residuals versus time, weighted residuals versus covariates, and histograms of estimated parameters were used together with the standard errors of the estimated parameter values to assess the goodness-of-fit.

In addition, exposures in terms of AUC_{inf} and C_{max} for each subject were estimated from the final model and compared between groups (*t* test).

RESULTS

The group mean observed escitalopram concentrations versus time after dosing is shown in Figure 1. The 2-compartment model with lag time gave the best fit, judged by the objective function values and visual inspection (results not shown), and became the base model. The base model (ADVAN4 and TRANS = 4 in NONMEM) was parameterized in terms of lag time (t_{lag}), absorption rate constant (k_a), apparent volume of distribution for the central compartment (V/F) and the peripheral compartment (V_2/F), oral clearance (CL/F), and distributional clearance (CLD2/F). Interindividual variability was modeled with exponential terms

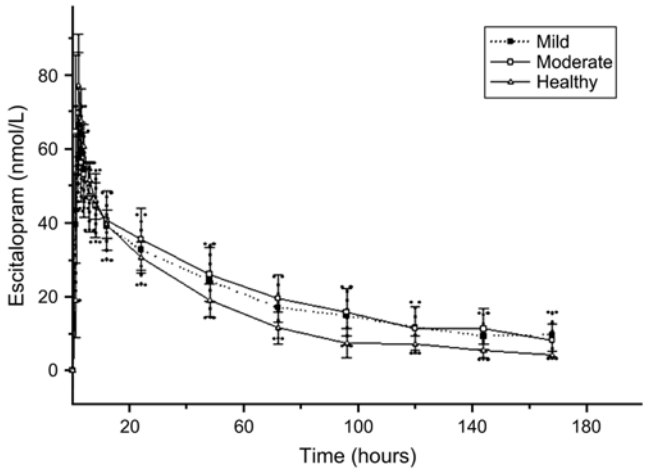

Figure 1. Mean (± standard deviation) observed escitalopram concentrations (nmol/L) versus time after dosing (h) for healthy, mild hepatic-impaired, and moderate hepatic-impaired subjects.

for V/F, CL/F, and k_a. A proportional model was used for the residual error. The value of the absorption rate constant, k_a, had to be fixed in order to run the model successfully. The value of k_a, set to 3.6 h^{-1}, was based on modeling the data from each subject separately (results not shown). Goodness-of-fit plots for the final model are given in Figure 2. Addition of weight on the central volume of distribution (V/F) and CYP2C19 activity on the clearance (CL/F) to the base model decreased the objective function significantly. Inclusion of Child-Pugh classification group significantly decreased the objective function value for the base model but to a lesser extent than inclusion of CYP2C19 activity did. When CYP2C19 was included in the expression for CL/F, addition of the Child-Pugh classification did not statistically significantly decrease the objective function value any further. Final expressions for volume (L) and clearance (L/h) for escitalopram were as follows:

$$V/F = 8.0 \cdot 10^2 + 12 \cdot (WT - 79) \quad (1)$$

$$CL/F = 19 - 17 \cdot (CYP2C19 - 0.769) \quad (2)$$

where WT is body weight in kg and CYP2C19 is the S/R-mephenytoin ratio. The "average" subject would have values for V/F and CL/F of $8.0 \cdot 10^2$ L and 19 L/h, respectively. No covariates were found to be significant for the other pharmacokinetic parameters. The significant covariates, WT and CYP2C19, are plotted versus the V/F and CL/F, respectively, values in Figure 3. The decrease of the OFVs per added covariate is given in Table 2. The interindividual variability estimates for V/F, CL/F, and k_a, respectively, were 24%, 44%, and 148%, respectively, for the base model (without covariates). For the final model, the variabilities were 17%, 34%, and 148%, respectively. Residual error was 9.6%. The values for all pharmacokinetic parameters, variability values, and errors are given in Table 3.

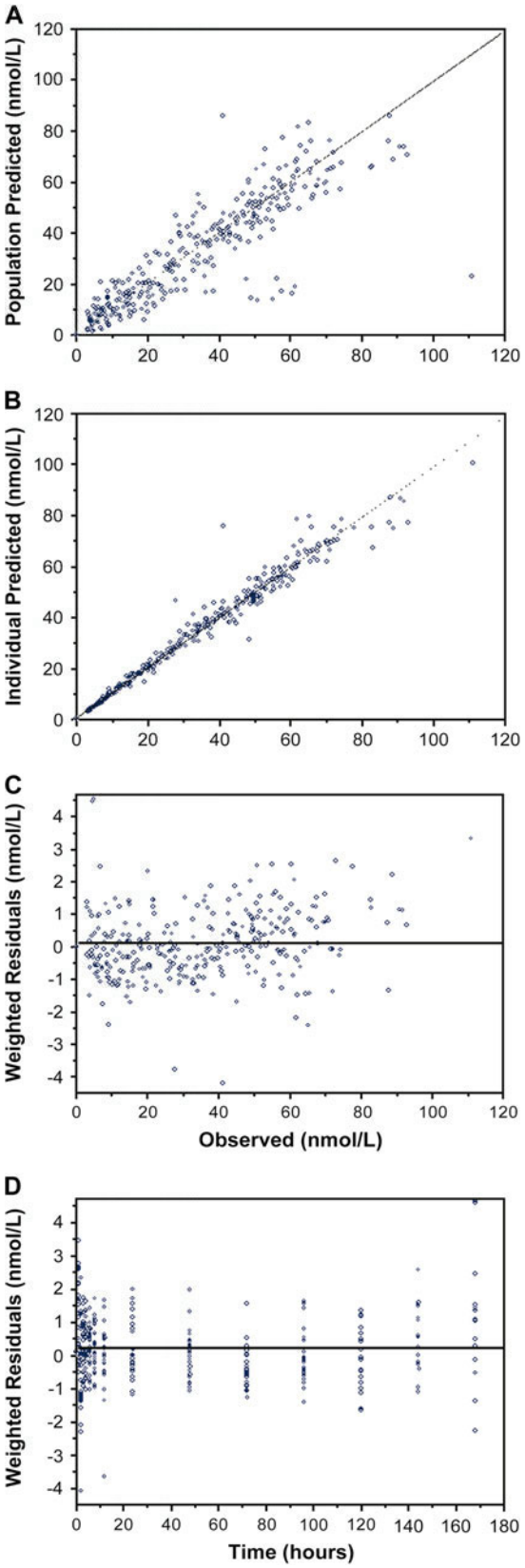

Figure 2. Final model. Scatter plot of predicted versus observed concentrations (a), Bayesian individually predicted versus observed concentrations (b), weighted residuals versus observed concentrations (c), and weighted residuals versus time after dosing (d).

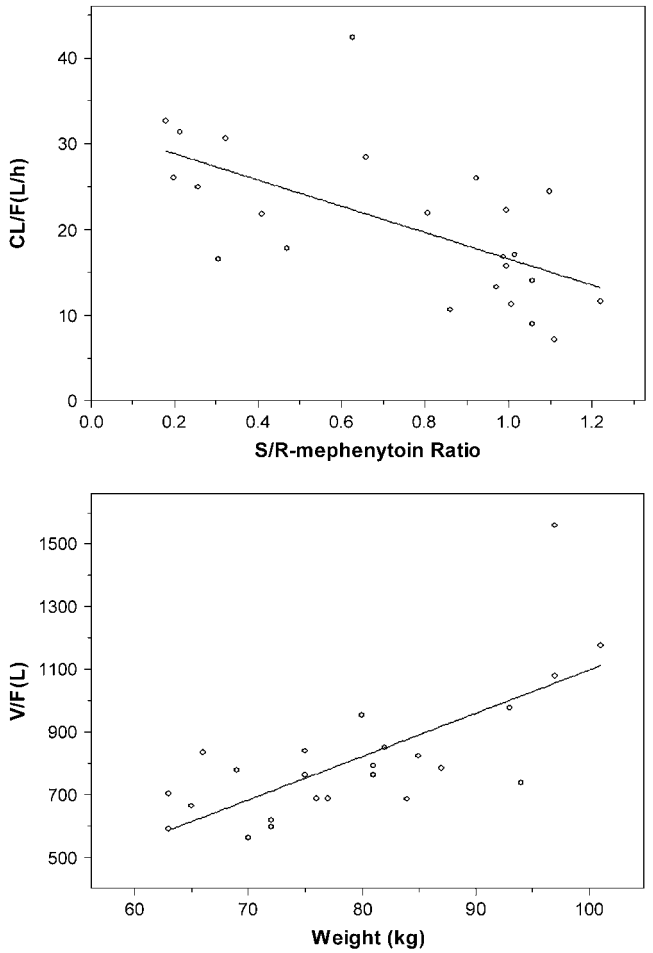

Figure 3. Final relationships for escitalopram between clearance (CL/F) and CYP2C19 capacity (expressed as S/R-mephenytoin ratio) and central volume of distribution (V/F) and body weight and with linear regression lines overlaid.

Model estimated mean group (Child-Pugh classification) CL/F values (± standard deviation [SD]) for escitalopram were 25.2 ± 6.1, 20.3 ± 10.9, and 16.2 ± 6.9 L/h for healthy, mild, and moderate hepatic impairment, respectively. Model estimated mean group (Child-Pugh classification) AUC_{inf} values (± SD) for escitalopram were $2.59 \cdot 10^3 \pm 6.98 \cdot 10^2$, $3.93 \cdot 10^3 \pm 2.26 \cdot 10^3$, and $4.38 \cdot 10^3 \pm 1.62 \cdot 10^3$ nM·h for healthy, mild, and moderate hepatic impairment, respectively. Comparison of CL/F and AUC_{inf} values between groups (*t* test) gave the following: healthy versus mild CL/F ($P = 0.37$), healthy versus moderate CL/F ($P = 0.015$), mild versus moderate CL/F ($P = 0.35$), healthy versus mild AUC_{inf} ($P = 0.14$), healthy versus moderate AUC_{inf} ($P = 0.013$), and mild versus moderate AUC_{inf} ($P = 0.75$). There were no significant differences in C_{max} between the groups.

Table 2. Statistically Significant ($P < .005$) Decreases in the OFV After Addition of Covariates to the Base Model*

Covariate Model	OFV (Decrease)
2-compartment with lag time (base model)	1217
Weight on V/F	1203 (–14)
Weight on V/F + CYP2C19 on CL/F	1190 (–13)

*OFV indicates objective function value.

Table 3. Final Parameter Values After Nonlinear Mixed Effect Modeling of the Pharmacokinetics of Escitalopram*

Parameter	Description	Unit	Value†	IIV† (%)
V/F		L	—	17 (34)
θ_1	Average V/F	L	$8.0 \cdot 10^2$ (6)	—
θ_7	Body weight on V/F	L/kg	12 (26)	—
CL/F		L/h	—	34 (25)
θ_2	Average CL/F	L/h	19 (7)	—
θ_8	CYP2C19 on CL/F	L/h	17 (23)	—
V_2/F (θ_3)		L	$4.7 \cdot 10^2$ (8)	—
CLD_2/F (θ_4)		L/h	98 (13)	—
k_a (θ_5)		h^{-1}	3.6 (fixed)	148 (31)
t_{lag} (θ_6)		h	0.93 (1)	—
Residual error, ϵ_1	Proportional error	%	9.6 (23)	—

*IIV indicates interindividual variability (%).
†The relative standard error is given as a percentage in parentheses.

Healthy subjects and those with mild or moderate hepatic impairment tolerated escitalopram well, and no serious adverse events were reported. Most adverse events were gastrointestinal in origin and were transient and either mild or moderate in intensity. No clinically significant changes in vital signs or hematology and clinical chemistry parameters were observed in any of the groups.

DISCUSSION

This study shows that CYP2C19 activity is a better predictor of the clearance of escitalopram than is the Child-Pugh classification. In other words, it may be more relevant to classify patients according to their CYP2C19 activity than it is to use the Child-Pugh classification when considering escitalopram exposure in hepatic-impaired subjects.

Although the absorption rate constant, k_a, had to be fixed during the model building, k_a values between subjects were allowed to vary because of interindividual variability. A sensitivity analysis was also performed where k_a varied in 10 intervals from 0.5 to 15 but the other parameter values were kept constant to the final model. This sensitivity analysis showed that the model was very stable also for different values on k_a. The percentage changes on the other parameter values ranged from 4% (on t_{lag} when $k_a = 2.5$) to –15% (on CLD2/F when $k_a = 2.5$).

Overall, the exposure results in this study with escitalopram in patients with hepatic impairment were similar to those seen previously with citalopram.[16] The approximately 2-fold increase in escitalopram AUC_{inf} in patients with hepatic impairment versus healthy subjects did not increase the incidence or severity of adverse events. The therapeutic recommended dose of escitalopram is 10 to 20 mg/day. In the present study, a single dose of escitalopram 20 mg was administered, as the resulting serum concentrations following this single dose were comparable to those seen after multiple dosing with escitalopram 10 mg, a dose frequently used in the clinic.

The present study indicates that escitalopram is well tolerated by patients with hepatic impairment and adds further evidence to the well-established safety profile observed clinically with escitalopram.

Conclusion

Patients with mild and moderate hepatic impairment had 51% ($P > .05$) and 69% ($P < .05$), respectively, higher AUC_{inf} values for escitalopram compared with healthy subjects. CYP2C19 activity is a better predictor of escitalopram clearance than Child-Pugh classification.

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